Answer 1:

Bibliographic Information

Efficacy of the quinocarmycins KW2152 and DX-52-1 against human melanoma lines growing in culture and in mice.
Plowman, Jacqueline; Dykes, Donald J.; Narayanan, Ven L.; Abbott, Betty J.; Saito, Hiromitsu; Hirata, Tadashi. Developmental Therapeutics Program, National Cancer Inst., Bethesda, MD, USA. Cancer Research (1995), 55(4), 862-7. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 122:151008 AN 1995:373656 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Quinocarmycin monocitrate (KW2152) and its analog, DX-52-1, demonstrated specificity for melanomas in the National Cancer Institute in vitro human tumor cell line drug screen. In contrast to most cell lines, a 50% redn. in tumor cell burden (as measured protein) at the end of a 48-h drug incubation was produced in five of eight melanoma lines by KW2152 concns. (LC50s) ranging from 0.49 to 10.93 μM and by DX-52-1 concns. ranging from 0.71 to 7.33 μM. Using the COMPARE algorithm, the patterns of differential cytotoxicity for both agents at the LC50 level of effect most closely resembled those for actinomycin D, mithramycin, and Adriamycin. In in vitro studies, both KW2152 (40 mg/kg/day) and DX-52-1 (90 mg/kg/day) caused partial and complete regressions of staged s.c.-implanted LOX IMVI melanoma xenografts following i.p. administration on days 5, 9, and 13 and produced tumor growth delays of 231 and 181%, resp. Activity was augmented by more prolonged therapy. Statistically significant growth inhibition of SK-MEL-2, UACC-62, UACC-257, and M14, but not SK-MEL-5 and MALME-3M, melanoma xenografts also was obsd. following every fourth or seventh day i.p. treatments. Based on these findings, DX-52-1 has been selected by the National Cancer Institute for development to clin. trial esp. against melanomas. This agent represents one of the first to be selected for preclin. development based on disease-panel specificity discovered in the National Cancer Institute cancer drug screen.

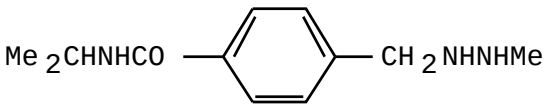
Answer 2:

Bibliographic Information

Treatment of five subcutaneous human glioma tumor lines in athymic mice with carmustine, procarbazine, and mithramycin.
Schold, S. Clifford; Bigner, Darell D. Med. Cent., Duke Univ., Durham, NC, USA. Cancer Treatment Reports (1983), 67(9), 811-19. CODEN: CTRRDO ISSN: 0361-5960. Journal written in English. CAN 99:98696 AN 1983:498696 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Five human glioma tumor lines were transplanted s.c. in athymic nude mice. Three of the lines (D-54 MG, U-118 MG, and U-251 MG) were derived from permanent human glioma cell lines, while the other 2 lines (N-456 and N-519) were established as direct xenografts in mice. Growth rates varied among the lines, but all were treated at a common av. tumor vol. of 200-300 mm3. Three drugs of known clin. activity against human anaplastic glial tumors were tested in this system. Procarbazine (PCB)(I) [671-16-9] produced significant responses in all 5 tumor lines, carmustine [154-93-8] produced significant growth delays in 2, and mithramycin (II) [18378-89-7] produced a slight growth delay in only 1. A carmustine-PCB combination produced a greater therapeutic effect than either agent alone against D-54 MG, but the combination was no more effective than PCB alone against U-118 MG. These results parallel clin. experience and indicate that this is a useful model for testing agents of potential activity in brain tumor therapy.



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Answer 3:

Bibliographic Information

SP1-regulated p27/Kip1 gene expression is involved in terbinafine-induced human A431 cancer cell differentiation: an in vitro and in vivo study. Huang Ching-Shui; Ho Wei-Lu; Lee Wen-Sen; Sheu Ming-Thau; Wang Ying-Jan; Tu Shih-Hsin; Chen Rong-Jane; Chu Jan-Show; Chen Li-Ching; Lee Chia-Hwa; Tseng How; Ho Yuan-Soon; Wu Chih-Hsiung Department of Surgery, Cathay Medical Center, Taipei, Taiwan Biochemical pharmacology (2008), 75(9), 1783-96. Journal code: 0101032. ISSN:0006-2952. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18355800 AN 2008258621 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In this study, the differentiation-promoting effects of terbinafine (Lamisil), TB) were investigated in human epithelioid squamous carcinoma (A431) cells. The polyhydroxyethylmethacrylate (poly-HEMA)- and type-I collagen-coated culture plate models were adapted to harvest the TB-induced differentiated cells by agitation of the suspension medium. We demonstrated that p27/Kip1, p21/Cip1 and the keratinocyte differentiation marker, human involucrin (hINV), were induced (>25 microM) in TB-induced differentiated A431 cells. Animal studies demonstrated that administration of TB (10 mg/kg body weight) inhibited A431-xenografted tumor growth through differentiation processes as evidenced by expression of pancytokeratin in tumor tissues. Immunocytochemical staining analysis showed that p27/Kip1, but not p21/Cip1, positive-stained cells were detected in the early-differentiated cells of TB-treated tumor tissues. SP1, which regulates p27/Kip1 expression, was induced by TB (>10 microM) in A431 cells. The TB-induced promoter activity and protein expression levels of p27/Kip1 were significantly attenuated by pretreatment with mithramycin A, a SP1 specific inhibitor. We also demonstrated that TB-induced differentiated A431 cells sorted from the poly-HEMA-coated culture plates were arrested in the G1 phase. TB-induced G1 arrest in the suspension-cultured cells was attenuated by mithramycin A pretreatment. Such results suggest that SP1 plays a critical role in the p27/Kip1 gene transcriptional activation that may be subsequently involved in the TB-induced A431 cancer cell differentiation process.

Answer 4:

Bibliographic Information

Therapeutic inhibition of Sp1 expression in growing tumors by mithramycin a correlates directly with potent antiangiogenic effects on human pancreatic cancer. Yuan Ping; Wang Liwei; Wei Daoyan; Zhang Jun; Jia Zhiliang; Li Qiang; Le Xiangdong; Wang Huamin; Yao James; Xie Keping Department of Pathology, Ruijin Hospital, Shanghai Jiaotong University, Shanghai, People's Republic of China Cancer (2007), 110(12), 2682-90. Journal code: 0374236. ISSN:0008-543X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17973266 AN 2007719523 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Human pancreatic cancer over expresses the transcription factor Sp1. However, the role of Sp1 in pancreatic cancer angiogenesis and its use as target for antiangiogenic therapy remain unexplored. METHODS: Archived human pancreatic cancer specimens were used to assess gene expression and microvessel density (MVD) status by immunohistochemistry: Small-interfering RNA (siRNA) was used to determine the impact of altered Sp1 expression on tumor growth and angiogenesis, and mithramycin A (MIT) was used to evaluate Sp1-targeted antiangiogenic treatment of human pancreatic cancer in animal models. RESULTS: The expression level of Sp1 was correlated directly with the MVD status ($P < .001$) and the expression level of vascular endothelial growth factor (VEGF) ($P < .05$). Knockdown of Sp1 expression did not affect the growth of pancreatic cancer cells in vitro but inhibited their growth and metastasis in mouse models. This antitumor activity was consistent with the in vitro and in vivo antiangiogenic activity resulting from Sp1 knockdown. Subcutaneous and intraperitoneal injection of MIT significantly suppressed the growth of human pancreatic cancer in mouse models. This tumor suppression was correlated with the suppression of Sp1 expression in growing tumors but not in normal tissues. Moreover, treatment with MIT reduced tumor MVD, which was consistent with the

down-regulation of VEGF, platelet-derived growth factor, and epidermal growth factor receptor. CONCLUSIONS: Both clinical and experimental evidence indicated that Sp1 is a critical regulator of human pancreatic cancer angiogenesis and the antitumor activity of MIT is a result, at least in part, of the suppression of Sp1 expression and consequent down-regulation the downstream targets of Sp1 that are key to angiogenesis. 2007 American Cancer Society

Answer 5:

Bibliographic Information

Molecular basis of the synergistic antiangiogenic activity of bevacizumab and mithramycin A. Jia Zhiliang; Zhang Jun; Wei Daoyan; Wang Liwei; Yuan Ping; Le Xiangdong; Li Qiang; Yao James; Xie Keping Department of Gastrointestinal Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA Cancer research (2007), 67(10), 4878-85. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) written in English. PubMed ID 17510417 AN 2007298567 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The impact of antiangiogenic therapy on the Sp1/vascular endothelial growth factor (VEGF) pathway and that of alteration of Sp1 signaling on the efficacy of antiangiogenic therapy is unclear, yet understanding their interactions has significant clinical implications. Treatment with bevacizumab, a neutralizing antibody against VEGF, suppressed human pancreatic cancer growth in nude mice. Gene expression analyses revealed that this treatment substantially up-regulated the expression of Sp1 and its downstream target genes, including VEGF and epidermal growth factor receptor, in tumor tissues, whereas it did not have this effect on pancreatic cancer cells in culture. Treatment with mithramycin A, an Sp1 inhibitor, suppressed the expression of Sp1 and its downstream target genes in both cell culture and tumors growing in nude mice. Combined treatment with bevacizumab and mithramycin A produced synergistic tumor suppression, which was consistent with suppression of the expression of Sp1 and its downstream target genes. Thus, treatment with bevacizumab may block VEGF function but activate the pathway of its expression via positive feedback. Given the fact that Sp1 is an important regulator of the expression of multiple angiogenic factors, bevacizumab-initiated up-regulation of Sp1 and subsequent overexpression of its downstream target genes may profoundly affect the potential angiogenic phenotype and effectiveness of antiangiogenic strategies for human pancreatic cancer. Therefore, this study is the first to show the significance and clinical implications of alteration of Sp1 signaling in antiangiogenic therapy for pancreatic cancer and other cancers.

Answer 6:

Bibliographic Information

Anti-tumour activity in non-small cell lung cancer models and toxicity profiles for novel ruthenium(II) based organo-metallic compounds. Guichard S M; Else R; Reid E; Zeitlin B; Aird R; Muir M; Dodds M; Fiebig H; Sadler P J; Jodrell D I Pharmacology and Drug Development Group, Cancer Research UK Centre, University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh EH4 2XR, UK Biochemical pharmacology (2006), 71(4), 408-15. Journal code: 0101032. ISSN:0006-2952. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 16360645 AN 2006025267 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Novel ruthenium(II) organo-metallic compounds are active in ovarian cancer models [Aird RE, Cummings J, Ritchie AA, Muir M, Morris RE, Chen H, et al. In vitro and in vivo activity and cross resistance profiles of novel ruthenium(II) organometallic arene complexes in human ovarian cancer. Br J Cancer 2002;86(10):1652-7]. [(eta6-C6H5C6H5)Ru(en)Cl]+ (as a PF6 salt, where en=ethylenediamine (RM175)) has been evaluated in a 13-cell line

panel. Particular sensitivity (approximately 10-fold lower than mean IC50) was noted in breast cancer and non-small cell lung cancer cell lines. In addition, IC50 in the A549 was 2 microM and RM175 (25 mg kg-1, days 1 and 5, i.p.) caused a significant (p=0.004) growth delay in a xenograft model. HC11 [(eta6-tetrahydroanthracene)Ru(en)Cl]PF6 was more potent in the A549 cell line (IC50 0.5 microM). HC11 (25 mg kg-1, days 1, 8 and 15, i.p.) was also active in vivo. Following RM175 25 mg kg-1, days 1 and 5, and 15 mg kg-1, days 1-5, HC11 25 and 40 mg kg-1, day 1, elevated alanine transaminase levels were detected, suggesting hepatotoxicity. No changes were observed in kidney or haematological parameters. In liver sections, multi-focal hepatic necrosis was seen, becoming confluent at high doses of HC11. In vitro studies confirmed that HC11 was more toxic than RM175 to fresh human hepatocytes and equitoxic to mithramycin. Liver toxicity may be related to the arene ligand and modification may reduce the potential for hepatic toxicity, while maintaining the anti-tumour activity seen.

Answer 7:

Bibliographic Information

Use of isogenic human cancer cells for high-throughput screening and drug discovery. Comment in: Nat Biotechnol. 2001 Oct;19(10):919-20. PubMed ID: 11581652 Torrance C J; Agrawal V; Vogelstein B; Kinzler K W The Howard Hughes Medical Institute, 1650 Orleans Street, Baltimore, MD 21231, USA Nature biotechnology (2001), 19(10), 940-5. Journal code: 9604648. ISSN:1087-0156. (EVALUATION STUDIES); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 11581659 AN 2001534514 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Cell-based screening for novel tumor-specific drugs has been compromised by the lack of appropriate control cells. We describe a strategy for drug screening based on isogenic human cancer cell lines in which key tumorigenic genes have been deleted by targeted homologous recombination. As a test case, a yellow fluorescent protein (YFP) expression vector was introduced into the colon cancer cell line DLD-1, and a blue fluorescent protein (BFP) expression vector was introduced into an isogenic derivative in which the mutant K-Ras allele had been deleted. Co-culture of both cell lines allowed facile screening for compounds with selective toxicity toward the mutant Ras genotype. Among 30,000 compounds screened, a novel cytidine nucleoside analog was identified that displayed selective activity in vitro and inhibited tumor xenografts containing mutant Ras. The present data demonstrate a broadly applicable approach for mining therapeutic agents targeted to the specific genetic alterations responsible for cancer development.